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EXAMINER	
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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Paper No. 1203

Application Number: 09/674,002
Filing Date: December 27, 2000
Appellant(s): BILLGER ET AL.

Stephen A. Bent
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed on September 24, 2003.

(1) Real Party in Interest

A statement identifying the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

A statement identifying the related appeals and interferences which will directly affect or be directly affected by or have a bearing on the decision in the pending appeal is contained in the brief.

(3) Status of Claims

The statement of the status of the claims contained in the brief is correct except Appellant fails to mention that claims 29 and 30 were withdrawn from further consideration, as being drawn to an unelected invention.

(4) Status of Amendments

Appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Invention

The summary of invention contained in the brief is essentially correct, except that there is no support in the specification for the statement, "...the parathyroid hormone present in such a formulation must remain stable as a liquid for many days".

(6) Issues

The appellant's statement of the issues in the brief is essentially correct.

(7) Grouping of Claims

Appellant's brief includes a statement that the claims stand or fall together.

(8) Claims Appealed

The copy of the appealed claims contained in the Appendix to the brief is correct.

(9) Prior Art of Record

- Holthuis et al., U.S. Patent 5,496,801, March 5, 1996.
- Endo et al., U.S. Patent 5,563,122, October 8, 1996.
- Selsted, M. E. U.S. Patent 5,547,939, August 20, 1996.

(10) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claim Rejections under 35 USC § 103 (a)

(i). The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

(ii) Claims 1-7, 9, 12, 17, 18, 21-24, 26-28, and 31-36 are rejected under 35 U.S.C. § 103 (a) as being unpatentable over Holthuis et al. (U.S. Patent 5,496,801, March 5, 1996) in view of Endo et al. (U.S. Patent 5,563,122, October 8, 1996).

Holthuis et al. teach a pharmaceutical formulation comprising human parathyroid hormone (1-84), mannitol as excipient, and citrate as buffering agent in both lyophilised and liquid form and a method for treating a bone related disorder, osteoporosis using the formulation (see, e.g., Abstract; column 4). The human parathyroid hormone (1-84) was obtained either recombinantly or by extraction from

human fluid (bottom of column 2). Holthuis et al. teach, for example, a formulation comprising human PTH (1-84) at 0.09 mg/ml to 2.27 mg/ml, 50 mg/ml mannitol, 10 mM citrate buffer at a pH between 4 and 6 (4th paragraph of column 6). This composition was prepared in liquid form and was then dried by lyophilization for long-term storage (5th paragraph of column 6). Holthuis et al. further teach that end-users can reconstitute the dried PTH with water. In the case where a multi-dose vial is provided, a bacteriostatic agent (i. e., a preservative) should be incorporated, and the formulation remaining after administration of each dose can be refrigerated for subsequent use within a time frame of several days (3rd paragraph of column 5).

Furthermore, Holthuis et al. teach that most compositions comprising PTH in the art are prepared in water-based vehicles such as saline (aqueous solution of NaCl; lines 34-35 of column 1).

Holthuis et al. fail to explicitly teach inclusion of sodium chloride (NaCl) in their pharmaceutical formulation.

Endo et al. teach that addition of sodium chloride, in the presence of mannitol, further stabilizes PTH (see, e.g., Table 2; Examples). Endo et al. teach a formulation comprising 2mg/ml sodium chloride and 20mg/ml mannitol (see Example 3). Endo et al. further teach that distilled water, physiological saline (aqueous solution of NaCl), or buffer solutions can be used to reconstitute the lyophilized composition comprising PTH (4th paragraph of column 2).

Therefore, it would have been obvious to one having ordinary skill in the art at the time the invention was made to reconstitute the dried composition comprising

PTH taught by Holthuis et al. with saline, which would yield a stable, liquid pharmaceutical composition comprising NaCl, with a reasonable expectation of success. One would have been motivated to do so because saline is one of the most commonly used pharmaceutically acceptable carriers, as taught by Endo et al. and Holthuis et al.

It would also have been obvious to one having ordinary skill in the art at the time the invention was made to include NaCl in the dried PTH formulation of Holthuis et al., with a reasonable expectation of success. One would have been motivated to do so because Endo et al. demonstrate that addition of sodium chloride, in addition to mannitol, further stabilizes PTH (see, e.g., Table 2). Reconstitution of the dried PTH formulation comprising NaCl with distilled water would yield a liquid pharmaceutical formulation comprising PTH and NaCl, which clearly reads on the instant claims.

(iii) Claims 20 and 25 are rejected under 35 U.S.C. § 103 (a) as being unpatentable over Holthuis et al. (U.S. Patent 5,496,801, March 5, 1996) in view of Endo et al. (U.S. Patent 5,563,122, October 8, 1996), as applied to claims 1-7, 9, 12, 17, 18, 21-24, 26-28, and 31-36 above, and further in view of Selsted (U.S. Patent 5,547,939, August 20, 1996).

Holthuis et al. and Endo et al. teach pharmaceutical formulations and methods of treating a bone related disorder, e.g., osteoporosis, with the formulations as applied to claims 1-7, 9, 12, 17, 18, 21-24, 26-28, and 31-36 above.

Neither Holthuis et al. nor Endo et al. teach the use of the specific preservatives, benzyl alchohol, m-cresol or EDTA in the pharmaceutical formulation.

Selsted teaches methods of inhibiting survival or growth of a microorganism using a composition comprising EDTA, which disrupts microbial membranes (1st paragraph of column 7).

Therefore, it would have been obvious to one having ordinary skill in the art at the time the invention was made to further include a preservative, e.g., EDTA, in the formulations taught by Holthuis et al. in combination with Endo et al. with a reasonable expectation of success. One would have been motivated to do so because Holthuis et al. teach a bacteriostatic agent (i. e., a preservative) should be incorporated where a multi-dose vial is provided, whereas Selsted teach that EDTA disrupts microbial membranes and inhibits survival or growth of a microorganism.

(11) Response to Argument

At the top of page 4 of the Brief, Appellant summarizes the requirement for establishing a *prima facie* case of obviousness under Section 103 (a). The Examiner does not disagree on these requirements.

At the second paragraph of page 4 the Brief, Appellant makes general statements that the subject matter of the present invention is not obvious and criticizes the Examiner for not considering evidence of record. The Examiner disagrees with

Appellant and maintains that the claimed invention is obvious over the teachings in the art for the reasons set forth in Section (10) immediately above.

At the bottom of page 4 of the Brief, Appellant summarizes the history of the rejection, which is essentially correct. The Examiner notes that the claims were amended to narrow the scope of invention by reciting "a *stable, liquid* pharmaceutical formulation of human parathyroid hormone" in response to the Final Office Action (Paper No. 12, March 24, 2003).

Beginning at the 2nd paragraph of page 5 of the Brief, Appellant argues that there is no teaching in the prior art of a stable liquid parathyroid hormone. Specifically, Appellant argues (i) that Examiners have misunderstood the cited prior art; (ii) that neither Endo et al. nor Holthuis et al suggested using sodium chloride in a liquid formulation of parathyroid hormone, and neither publication provides any reason or motivation for the skilled artisan to have made this modification; and (iii) Holthuis et al was not concerned with, and did not address, the stability of a liquid parathyroid hormone that contained sodium chloride (bottom of page 5 to top of page 6).

Appellant's arguments have been fully considered, but are not deemed to be persuasive for the following reasons. Firstly, there is no clear definition for the term "stable" in the specification. The Examiner fails to find the specific support in the specification for the assertion in the Brief, "...the parathyroid hormone present in such a formulation must remain stable as a liquid for many days" (bottom of page 1 of the

Brief). It is also noted that Applicants fails to acknowledge in the specification that it was totally unexpected that Appellants' liquid composition, containing both chloride ion and highly concentrated parathyroid hormone, lacked the undesirable traits predicted by the conventional wisdom (end of 1st paragraph of page 3 of the Brief).

Secondly, Appellant's criticism that both Examiners have misunderstood the cited prior art is incorrect (detailed below). Thirdly, Holthuis et al. teach a pharmaceutical formulation comprising human parathyroid hormone (1-84), mannitol as excipient, and citrate as buffering agent in both lyophilised and liquid form and a method for treating a bone related disorder, osteoporosis using the formulation (see, e.g., Abstract; column 4). Holthuis et al. teach, for example, a formulation comprising human PTH (1-84) at 0.09 mg/ml to 2.27 mg/ml, 50 mg/ml mannitol, 10 mM citrate buffer at a pH between 4 and 6 (4th paragraph of column 6). This composition was prepared in liquid form and was then dried by lyophilization for long-term storage (5th paragraph of column 6). Holthuis et al. further teach that end-users can reconstitute the dried PTH with water. In the case where a multi-dose vial is provided, the formulation remaining after administration of each dose can be refrigerated for subsequent use within a time frame of several days (3rd paragraph of column 5). Thus, Holthuis et al. teach a liquid PTH formulation, which is stable for several days. Clearly, the statement in title of section A, (ii), "there is no teaching in the prior art of a stable liquid parathyroid hormone" is incorrect.

Furthermore, the cited art provides motivation for an artisan to include NaCl in the PTH formulation in liquid form. As noted above, Holthuis et al. teach that most

compositions comprising PTH are prepared in water-based vehicles such as saline (aqueous solution of NaCl; lines 34-35 of column 1). Endo et al. teach that physiological saline (aqueous solution of NaCl) among others can be used to reconstitute the lyophilized composition comprising PTH (4th paragraph of column 2). It would have been obvious to an artisan at the time the invention was made to reconstitute the dried composition comprising PTH taught by Holthuis et al. with saline, which would yield a stable, liquid pharmaceutical composition comprising NaCl, with a reasonable expectation of success. One would have been motivated to do so because saline is one of the most commonly used pharmaceutically acceptable carriers, as taught by Endo et al. and Holthuis et al.

It would also have been obvious to one having ordinary skill in the art at the time the invention was made to include NaCl in the dried PTH formulation of Holthuis et al., with a reasonable expectation of success. One would have been motivated to do so because Endo et al. demonstrate that addition of sodium chloride, in addition to mannitol, further stabilizes PTH (see, e.g., Table 2). Reconstitution of the dried PTH formulation comprising NaCl with distilled water would yield a liquid pharmaceutical formulation comprising PTH and NaCl, which obviously reads on the instant claims.

The Examiner notes that the contradictory art (Matindale, the Extra Pharmacoepia, The Pharmaceutical Press, London, 29th Edition, 1989 at p.1338; CA 2,234,724) recited by Appellant, will be considered in detail later in this Answer.

Beginning at the 2nd paragraph of page 6 of the Brief, Appellant argues that informed by Endo et al., the skilled artisan might have been motivated to add sodium chloride and sugar to Holthuis' freeze-dried parathyroid hormone. To have arrived at Appellant's claimed invention, however, the skilled artisan would have been prompted to add sodium chloride and sugar to Holthuis' parathyroid hormone and would have been motivated to retain and store that mixture in liquid form.

Appellant's argument has been fully considered but is not deemed to be persuasive for the following reasons. First, the PTH formulation of Holthuis et al. comprises mannitol, the most preferred monosaccharide taught by Endo et al. (top of column 2). Thus, addition of mannitol to the PTH formulation of Holthuis et al. is not needed. Secondly, since an artisan is motivated to add sodium chloride to Holthuis' freeze-dried parathyroid hormone in view of the teaching of Endo et al., as Appellant acknowledged (beginning of the second paragraph of page 6 of the Brief), reconstitution of the formulation with distilled water would yield a liquid pharmaceutical formulation comprising PTH and NaCl, which reads on the limitations of claims. Appellant is reminded that the claims are drawn to a composition, not a method of making the composition. It does not alter the composition itself when and how the composition becomes liquid form.

Alternatively, an artisan would be motivated to reconstitute the dried composition comprising PTH taught by Holthuis et al. with saline, which would yield a liquid pharmaceutical composition comprising NaCl, as saline is one of the most commonly used pharmaceutically acceptable carriers, as taught by Holthuis et al. and Endo et al.

As noted above, Holthuis et al. teach that where a multi-dose vial is provided, the PTH formulation remaining after administration of each dose can be refrigerated for subsequent use within a time frame of several days (3rd paragraph of column 5). Either way, the claimed invention is obvious over the prior art.

Beginning at the bottom of page 6 of the Brief, Appellant argues that the conventional wisdom, as evidenced in the cited art, taught away from creating a highly concentrated parathyroid hormone liquid that contained sodium chloride. Specifically, Appellant argues Holthuis references "Martindale: the Extra Pharmacopeia", which teaches away from incorporating parathyroid hormone in a sodium chloride solution.

Appellant's argument has been fully considered but is not deemed to be persuasive for the following reasons. First, The Examiner would like to point out that while Appellant claims that the reference of Martindale was provided to the Office in response to the final Office Action, the fact is that Appellant never did. Only when the Examiner telephoned the Appellant and requested a copy of the reference on December 4, 2003, did Appellant fax a copy of the reference to the Examiner.

Secondly, as Appellant argues, the reference of Martindale states that "solutions of parathyroid hormone may be diluted with glucose 2.5 to 5.0%. Sodium chloride solutions should not be used as they often cause precipitation." However, It should be noted that the stability of a protein in aqueous solution is influenced by many factors, such as concentration of the protein, pH, temperature, types of ions, ionic strength (concentration), presence of gases (e.g., O_2), and time. Thus, Martindale's teaching is limited to his own dried parathyroid; Martindale does not teach, in any means, that

saline cannot be used to reconstitute dried Parathyroid formulation taught by Holthuis et al., which comprises, e.g., human PTH (1-84) at 0.09 mg/ml to 2.27 mg/ml, 50 mg/ml mannitol, 10 mM citrate buffer at a pH between 4 and 6 (4th paragraph of column 6). In addition, whether NaCl causes precipitation of parathyroid in a particular formulation can be readily determined and an artisan can decide, as a choice, to use saline, distilled water, or other water-based vehicles. Therefore, the brief report of Martindale does not teach away from using saline in other parathyroid formulations and cannot be used as a basis to deny the teachings of the general art.

In addition, the Examiner notes that Appellant's assertion, "it was well established that *presence of sodium chloride in such a liquid can cause precipitation of highly concentrated proteins*" (bottom of page 6 of the brief), is incorrect. This is because, as noted above, precipitation of a protein in an aqueous solution depends on numerous factors. A trace amount of sodium chloride or any salts would not cause a protein to precipitate; on the other hand, an unlimited amount (extremely high concentration) of sodium chloride or any salts would cause any proteins to precipitate. Thus, it is the concentration of a salt (ionic strength), among others, that influences the solubility of a protein in an aqueous solution. In this regard, it is also noted that claim 1 and its dependent claims have no limitations on the concentration of NaCl. Consequently, Appellants' assertion, "Appellants' liquid composition, containing both chloride ion and highly concentrated parathyroid hormone, lacked the undesirable traits predicted by the conventional wisdom" (last sentence of 1st paragraph of page 3 of the brief), is obviously erroneous.

Furthermore, Appellant's argument that Holthuis et al. cited Martindale's reference for not using saline in their parathyroid formulation is misleading. To be illustrative, the exact statement of Holthuis et al. when Martindale's reference is cited is reproduced here: "There is also an International Reference preparation which for human PTH consists of 100 ng of hormone ampouled with 250 μg human serum albumin and 1.25 mg lactose, and for bovine PTH consists of 10 μg lyophilized hormone in 0.01M acetic acid and 0.1% w/v mannitol (see Matindale, the Extra Pharmacoepia, The Pharmaceutical Press, London, 29th Edition, 1989 at p.1338)." It is clear that Holthuis et al. cites Martindale's reference for the purpose of reviewing various PTH formulations. There is no teaching that NaCl cannot be used to reconstitute the dried formulation taught by Holthuis et al. In fact, Holthuis et al. clearly point out, in the same paragraph where the Martindale's reference is cited (4th paragraph of column 1), that *most PTH preparations in the art are prepared in water-based vehicles such as saline*, or water acidified typically with acetic acid to solubilize the hormone (lines 32-37 of column 1). Holthuis et al. further cites a reference of Hodsman et al. where a human PTH preparation was reconstituted in saline (lines 53-55).

Therefore, physiological saline (aqueous solution of NaCl) is a widely accepted carrier for reconstitution of PTH formulations and provides a choice as a water-based vehicle to dissolve PTH formulations.

Beginning at the bottom of page 7 of the Brief, Appellant argues that Canadian patent application, CA 2,234,724 taught that sodium chloride, even in lyophilized preparations, causes undesirable dimerization of parathyroid hormone.

Appellant's argument has been fully considered but is not deemed to be persuasive for the following reasons. First, as noted immediately above, the stability of a protein is influenced by many factors. A protein can be stable for a few days under certain conditions, but may not be stable for a few weeks, a few months, or a few years. The specification fails to define the term "stable" unambiguously whereas the claims fails to recite a specific period in term of "stable". The teaching of Canadian patent application, CA 2,234,724 is limited to the lyophilized parathyroid preparation comprising sucrose and NaCl stored after 1 or 3 months (Example 7 and Table 1). CA 2,234,724 does not teach the stability of PTH preparation over a storage period of a few days; CA 2,234,724 does not teach, in any means, that saline cannot be used to reconstitute dried Parathyroid formulation taught by Holthuis et al., which comprises, e.g., human PTH (1-84) at 0.09 mg/ml to 2.27 mg/ml, 50 mg/ml mannitol, 10 mM citrate buffer at a pH between 4 and 6 (4^{th} paragraph of column 6).

Secondly, careful examination of Example 7 and the data summarized in Table 1 of Canadian patent application CA 2,234,724 does not support the statement that lyophilized parathyroid hormone made with sodium chloride shows a lower PTH content after a storage period of one or three months. In fact, the PTH content stored at 4^0c or 50 ^{0}c for one or three months is the highest among various conditions: the PTH content stored at 4^0c or 50 ^{0}c for one months is 100.9% (98.9/98.0 x 100) and 100.6%

(98.6/98.0 x 100), respectively, whereas the PTH content stored at 4^0c or 50 ^{0}c for three months is 100.9% (98.9/98.0 x 100) and 100.6% 98.6/98.0 x 100), respectively. These estimations (calculated by the Examiner) clearly indicate that there was no loss of PTH at all when compared with the staring material under the experimental conditions.

In addition, while there is an indication that the formation of PTH dimers occurred after a storage period of one or three months, there was no quantitative data available for an artisan to evaluate. More importantly, there were absolutely no teachings on the formation of PTH dimers when the PTH preparation was stored over a few days, either in a liquid form or a lyophilized form.

For the above reasons, the negative teaching by the Canadian patent application CA 2,234,724 does not, in Examiner's opinion, discourage an artisan from using physiological saline (aqueous solution of NaCl) for reconstitution of PTH formulations taught by Holthuis et al. in view of the general, positive teaching in the art, e.g., by Holthuis et al. (and the references cited by Holthuis et al.) or by Endo et al., as noted above. The reconstitution of such a PTH pharmaceutical formulation with saline would yield a stable, liquid PTH formulation, which reads on the instant claims.

Beginning at the bottom of page 8 of the Brief, Appellant criticizes the Examiner for failing to base the ultimate determination of patentability on the entire record. Specifically, Appellant criticizes the Examiner for dismissing the evidence (CA 2,234,724) by stating in the final Office Action, "while the Canadian patient CA 2,234,724 may teach a formulation preferably free of chloride ions, the majority of the

art teach the use of saline (the aqueous solution of sodium chloride) as a water-based vehicle and the use of mannitol as an excipient in a formulation comprising human parathyroid hormone (see, e.g., column 1, U.S. Patent 5,496,801, March 5, 1996)", but citing no other references except for Holthuis et al. Appellant further submits that even though Appellants provided the Examiner with a copy of the Martindale reference in response to the final Office Action, the Examiner appears to have dismissed entirely the teachings of Martindale. The Advisory Action is silent on the impact of Martindale.

Appellant's argument has been fully considered but is not deemed to be persuasive for the reasons set forth above.

Appellant concludes this section by urging that the rejection of claims under 35 U.S.C. § 103 (a) be reversed. The Examiner believes that the rejections should be sustained for the reasons set forth above.

Therefore, for reasons set forth above, Appellant's arguments have been fully and carefully considered, but are not deemed to be sufficient to rebut the prima facie case of obviousness rejection.

Respectfully submitted,

Ruixiang Li, Ph.D.
December 14, 2003
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